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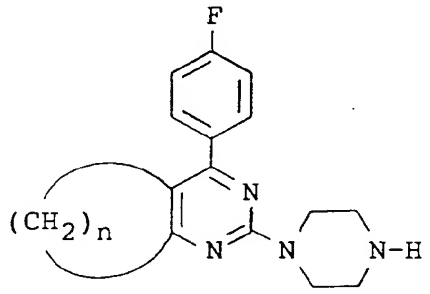
(71) Applicant: **DAINIPPON PHARMACEUTICAL CO., LTD.**
6-8, Doshomachi 2-chome Chuo-ku
Osaka-shi, Osaka 541(JP)

(72) Inventor: **Hino, Katsuhiko**
8-11, Shiroyamadai 3-chome Sango-cho
Ikoma-gun, Nara-ken(JP)
Inventor: **Kai, Naoki**
36-12, Nishikoya 2-chome
Amagasaki-shi, Hyogo-ken(JP)
Inventor: **Sakamoto, Masato**
3-3-103, Sonehigashimachi 2-chome
Toyonaka-ski, Osaka-fu(JP)
Inventor: **Kon, Tatsuya**
10-4, Kurekawa-cho
Ashiya-shi Hyogo-ken(JP)
Inventor: **Oka, Makoto**
17-26, Takada-cho
Ibaraki-shi, Osaka-fu(JP)
Inventor: **Furukawa, Kiyoshi**
12-4, Onosuimei 2-chome, Shiga-cho
Shiga-gun, Shiga-ken(JP)
Inventor: **Ochi, Yoshiaki**
2-4-611, Kitamidorigaoka 1-chome
Toyonaka-shi Osaka-fu(JP)

(74) Representative: **Kraus, Walter, Dr. et al**
Patentanwälte Kraus, Weisert & Partner
Thomas-Wimmer-Ring 15
W-8000 München 22(DE)

(54) **2-(1-piperazinyl)-4-phenylcycloalkanopyrimidine derivatives and pharmaceutical composition containing the same.**

(57) Novel 2-(1-piperazinyl)-4-phenylcycloalkanopyrimidine derivatives of the formula:



(I)

wherein n is 3, 5 or 6, or a pharmaceutically acceptable acid addition salt thereof, which is useful for the treatment of the cerebral insufficiency diseases.

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This invention relates to novel 2-(1-piperazinyl)-4-phenylcycloalkanopyrimidine derivatives useful as an active ingredient for the treatment of the cerebral insufficiency diseases and a pharmaceutical composition containing the said compound as an active ingredient.

Prior Art

There have hitherto been known some 2-(1-piperazinyl)-4-phenylcycloalkanopyrimidine derivatives and related compounds which have pharmacological activities. For example, Japanese Patent First Publication (Kokai) No. 5692875 discloses that 4-phenyl-2-(1-piperazinyl)quinazolines have anti-depressant activity. U.S. Patent 3,305,553 discloses that 2-(4-methyl-1-piperazinyl)-4-phenyl-quinazolines have anti-inflammatory activity, analgesic activity and anti-allergic activity, and further discloses the starting 2-(4-methyl-1-piperazinyl)-4-phenyl-5,6,7,8-tetrahydroquinazolines but does not mention any pharmacological activity thereof.

Besides, U.S. Patent 3,915,976 discloses that 2-[4-(C_1-C_4)alkyl-1-piperazinyl]-4-phenyl(C_5-C_8)-cycloalkanopyrimidines such as 6,7,8,9-tetrahydro-2-(4-methyl-1-piperazinyl)-4-phenyl-5H-cyclohepta[d]-pyrimidine and 6,7-dihydro-2-(4-methyl-1-piperazinyl)-4-phenyl-5H-cyclopenta-[d]pyrimidine have anti-inflammatory activity.

Moreover, it is disclosed in Chem. Pharm. Bull., 31, 2254-2261 (1983) that 4-phenyl-2-(1-piperazinyl)-5,6,7,8-tetrahydroquinazoline and 4-phenyl-2-(4-benzyl-1-piperazinyl)-5,6,7,8-tetrahydroquinazolinehave weak hypoglycemic activity.

However, there is no report as to the activity on the central nervous system of these 2-(1-piperazinyl)-4-phenylcycloalkanopyrimidine derivatives.

On the other hand, EP-A-0302967 discloses that 2-(4-allyl-1-piperazinyl)-4-pentyloxyquinazoline is useful as a remedying agent for cerebral dysfunction. But, the compounds of the present invention are structurally quite different from the compound of EP-A-0302967.

Moreover, EP-A-0022481 discloses that 2-piperazino-4-substituted-5,6-alkylenepyrimidine derivatives show an anti-hypertensive effect, an anti-inflammatory effect, a blood sugar level lowering effect, a blood platelet aggregation suppressive effect, and anorexigenic action and a serotonin effect.

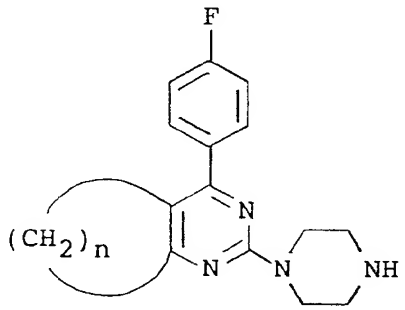
Brief Description of the Invention

The present inventors have extensively searched for compounds having an activity on the central nervous system and have found that novel 2-(1-piperazinyl)-4-phenyl-cycloalkanopyrimidine derivatives of the formula (I) disclosed hereinafter have excellent cerebral function improving activity and are useful as an active ingredient of a cerebral function improving medicament.

An object of the invention is to provide novel 2-(1-piperazinyl)-4-phenylcycloalkanopyrimidine derivatives having excellent activity for treating cerebral insufficiency diseases. Another object of the invention is to provide a pharmaceutical composition being useful as an agent for treating the cerebral insufficiency diseases containing said compound as an active ingredient. These and other objects and advantages of the invention will be apparent to those skilled in the art from the following description.

Detailed Description of the Invention

The novel 2-(1-piperazinyl)-4-phenylcycloalkanopyrimidine derivative of the present invention have the following formula (I):



(I)

wherein n is 3, 5 or 6, or a pharmaceutically acceptable acid addition salt thereof.

The salt of the compounds includes salts of inorganic acids (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc.), and salts of organic acids (e.g. maleate, fumarate, citrate, tartrate, lactate, benzoate, methanesulfonate, etc.). Besides, these salts may optionally be present in the form of a hydrate, and hence, the compounds of the present invention include also these hydrate compounds.

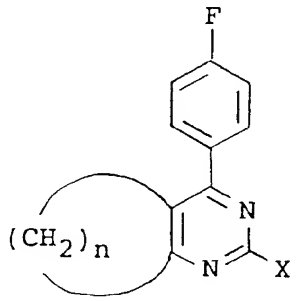
The specific compounds of the formula (I) are as follows.

2-(1-Piperazinyl)-4-(4-fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidine

2-(1-Piperazinyl)-4-(4-fluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine

2-(1-Piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclooctapyrimidine

The compounds of the formula (I) can be prepared, for example, by reacting a compound of the formula (II):



(II)

wherein X is a leaving atom or group and n is as defined above, with piperazine.

The leaving atom or group X in the formula (II) denotes any atom or group which can leave off in the form of HX under the reaction conditions together with hydrogen atom bonded to the nitrogen atom at 1-position of piperazine. Examples of the leaving atom or group are halogen atoms, lower alkylthio groups (e.g. methylthio, ethylthio, propylthio, butylthio, etc.), arylsulfonyloxy groups (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, etc.), and alkylsulfonyloxy groups (e.g. methanesulfonyloxy, etc.).

The reaction of the compound of the formula (II) and piperazine is carried out in an appropriate solvent or without using any solvent. Suitable examples of the solvent are aromatic hydrocarbons (e.g. toluene, xylene, etc.), ketones (e.g. methyl ethyl ketone, etc.), ethers (e.g. dioxane, diglyme, etc.), alcohols (e.g. ethanol, isopropyl alcohol, butanol, etc.), N,N-dimethylformamide, dimethyl sulfoxide. The reaction is preferably carried out in the presence of a basic substance. Suitable examples of the basic substance are alkali metal carbonates (e.g. sodium carbonate, potassium carbonate, etc.), alkali metal hydrogen carbonates (e.g. sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), tertiary amines (e.g. triethylamine, but an excess amount of piperazine may be used instead of using the basic substance. Piperazine may be used in the form of a hydrate. The reaction temperature is usually in the range of 40 to 200 °C. The starting compound (II) can be prepared in the procedure as described in Reference Examples 1 and 4 hereinafter or in a similar process.

The compounds of the formula (I) can be isolated and purified from the reaction mixture by a conventional method.

The compounds of the formula (I) are obtained in the form of a free base or a salt or a hydrate depending on the kinds of the starting compound, the reaction conditions, and the like. When the compounds are obtained in the form of a salt, they can be converted into the corresponding free base by a conventional method, for example, by treating them with a basic substance such as an alkali metal hydroxide. Besides, when the compounds are obtained in the form of a free base, they can be converted into the corresponding salt by a conventional method, for example, by treating them with various acids.

The compounds of the formula (I) of the present invention show excellent improving effects on behavioral and memory deficites induced by scopolamine or cycloheximide and a distinctive protective effect on hypoxia-induced death in animals. The compounds also selectively bind to serotonin (5-HT_2) receptor and increase in concentrations of a brain serotonin metabolite (5-HIAA). Accordingly, the compounds of the present invention can be used for the treatment of various symptoms of cerebral insufficiency.

That is, the compounds of the formula (I) of the present invention are useful as a medicament for the treatment of various symptoms of cerebral insufficiency, in dementia of Alzheimer's type, multi-infarct dementia, and other cerebrovascular dementia, and some other organic and functional brain disorders.

The pharmacological activities of the compounds of the present invention are illustrated by the following Experiments.

The test compounds used in the following Experiments are as follows:

Compound A: 2-(1-Piperazinyl)-4-(4-fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidine maleate (compound of Example 1)

Compound B: 2-(1-Piperazinyl)-4-(4-fluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine maleate (compound of Example 2)

Compound C: 2-(1-Piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclooctapyrimidine maleate (compound of Example 3)

Experiment 1

Antagonistic effect on scopolamine-induced hypermotility:

A group of 5 male mice (Std-ddy strain, 22 - 28 g) was used for examining effect of the test compounds on scopolamine-induced hypermotility, wherein the compound enhancing cholinergic neurotransmission was proved to have an antagonistic effect.

A test compound was orally administered to each mouse, mouse, and 90 minutes after the administration, each test animal was placed within a test cage (25 x 35 x 30 cm). After 30 minutes, scopolamine hydrobromide (1 mg/kg) was intraperitoneally administered to the mice and then the motility was measured with Animex activity meter for 30 minutes. The effect of test compounds was expressed as % antagonism (complete antagonism to the motility level of non-dosed animals = 100 %). The results are shown in the following Table 1.

Table 1

Antagonistic effect on scopolamine-induced hypermotility		
Test compound	Dose (mg/kg)	Inhibitory ratio (%)
Compound A	3	60.7
Compound B	30	69.2
Compound C	3	50.6

Experiment 2

Improving effect on scopolamine-induced deficit of spontaneous alternation behavior:

A group of 15 - 25 male mice (Std-ddY strain, 22 - 28 g) was used for evaluating effect of the test compounds on scopolamine-induced deficit of spontaneous alternation in a T-maze, which is a known animal model of memory impairment due to hypofunction of the cholinergic nervous system. The T-maze used consists of a stem and two arms which are 25 cm long, 5 cm wide and 10 cm high. The first 10 cm of the stem and last 10 cm of each arm are divided by sliding doors into start and goal boxes.

A test compound and scopolamine hydrobromide (1 mg/kg) were intraperitoneally administered to each mouse, and after 30 minutes a test of spontaneous alternation task in the T-maze was continuously repeated for 8 trials. Commonly, naive mice alternate each (right and left) goal box in turn, but scopolamine-treated animals tend to enter the same goal box repeatedly. The effect of the test compounds was expressed as % improvement (complete improvement to the alternation level of non-dosed mice = 100 %). The results are shown in Table 2.

Table 2

Improving effect on scopolamine-induced deficit of spontaneous alternation behavior		
Test compound	Dose (mg/kg)	Improvement (%)
Compound A	0.02 0.5	47.8 51.9
Compound B	2.0	39.1
Compound C	2.0	63.0

Experiment 3

Improving effect on cycloheximide-induced amnesia of passive avoidance response:

Anti-amnesic effect of the test compounds was examined using mice given cycloheximide which is a known amnesia-inducing agent.

A group of 15 - 20 male mice (Std-ddY strain, 27 - 33 g) was subjected to training and retention trials for a passive avoidance task in a step-down apparatus (30 x 30 x 50 cm) with a grid floor and a wooden platform (4 x 4 x 4 cm) in a center of the floor. In the training trial, each mouse was first placed on the platform, and when the mouse stepped down on the grid floor, an electric shock (1 Hz, 0.5 sec, 60 VDC) was delivered to the feet for 15 seconds. Immediately after the training trial, cycloheximide (60 mg/kg, s.c.) and a test compound (i.p.) were administered. The retention trial was carried out 24 hours thereafter, and the time from placing again each mouse on the platform until stepping down on the grid floor (step-down latency) was measured. The step-down latency in the retention trial was markedly shortened by treatment of cycloheximide (amnesia). The effect of test compounds was assessed by % improvement (complete improvement to the latency level of non-dosed animals = 100 %). The results are shown in Table 3.

Table 3

Improving effect on cycloheximide-induced amnesia of passive avoidance response		
Test compound	Dose (mg/kg)	Improvement (%)
Compound A	0.5 2.0	33.8 65.8
Compound B	0.5 2.0	93.7 72.8
Compound C	0.5	67.1

Experiment 4

Protective effect on sodium nitrite-induced anemic hypoxia:

It is known that sodium nitrite ($NaNO_2$) induces anemic hypoxia by converting hemoglobin to metohemoglobin, resulting in a severe impairment of brain function and ultimately in death. Based on the above knowledge, prolongation of survival time after sodium nitrite treatment was used as an index for antihypoxic effect of the test compounds.

A group of 20 male mice (Std-ddY strain, 25 - 30 g) was intraperitoneally given a test compound (10 mg/kg), and 2 hours after the treatment with the test compound, a lethal amount (225 mg/kg) of sodium nitrite was intraperitoneally administered, and then, the survival time of each mouse was measured. The effect of the test compounds was assessed by the prolongation rate (%) of survival time compared with that of the animals treated with sodium nitrite alone.

The prolongation rate of compound A was 36.7 %.

Experiment 5

Effect of binding to dopamine (D_2), serotonin (S_1, S_2) and adrenaline (α_1) receptor (in vitro receptor binding assay):

Dopamine (D_2), serotonin (S_1, S_2) and adrenaline (α_1) receptor binding assays were carried out according to the methods of I. Creese et al. [Eur. J. Pharmacol., 46, 377 (1977)], S. J. Peroutka et al. [Mol. Pharmacol., 16, 687 (1979)], J. E. Leysen et al. [Mol. Pharmacol., 21, 301 (1982)], and D. C. U'Prichard et al. [Mol. Pharmacol., 13, 454 (1977)], respectively.

Crude synaptosome fractions prepared from some brain regions in rats were used as the receptor sources, and [^{3}H] spiperone (D_2), [^{3}H] serotonin (S_1), [^{3}H] ketanserin (S_2) and [^{3}H] WB-4101 (α_1) were used as the labelled ligands. The binding assay was performed by incubating aliquots of synaptosome fraction in buffer solution (final volume 1 ml) containing the receptor source and the labelled ligand in the presence of a test compound having various concentration thereof for a fixed time. The assay was terminated by rapid filtration through Whatman GF/B glass fiber filters attached to a cell-harvester (Brandel) and radioactivity on the filters was counted with a scintillation counter. Specific binding was calculated as a difference between the amount of radioactivity in the assay group and that in the control group which was separately measured likewise in the presence of an excess amount of an unlabelled ligand [spiperone (D_2), serotonin (S_1), methysergide (S_2) and prazosin (α_1)] instead of the labelled ligand. The IC_{50} value of the test compounds (i.e. the concentration causing 50 % inhibition of the labelled ligand specific binding) was determined by probit analysis. The results are shown in Table 4.

Table 4

Binding effect to dopamine (D_2), serotonin (S_1, S_2) and adrenaline (α_1) receptor:				
Test compound	IC_{50} (nM)			
	D_2	S_1	S_2	α_1
Compound A	920	750	29	1100
Compound B	750	3000	9.6	3400
Compound C	130	1300	19	1200

Experiment 6

Increasing effect on concentration of brain serotonin metabolite:

A group of 5 male mice (Std-ddy strain, 25 - 30 g) was used for examining effect of the test compounds on concentration of a brain serotonin metabolite, 5-hydroxy-indole-3-acetic acid (5-HIAA). It is generally known that an increase in 5-HIAA is mainly caused by serotonin receptor blockade.

Mice were killed by decapitation two hours after the treatment with the test compounds. Brains were quickly taken out, homogenized in 1N formic acid-acetone solution, and centrifuged in a refrigerated ultracentrifuge. The supernatant was evaporated by blowing with N_2 gas, and then, the residue was again dissolved in 0.01N acetic acid, and served for determining 5-HIAA concentration by high performance liquid chromatography with electrochemical detection. The effect of the test compounds on 5-HIAA concentration was shown as % of control (5-HIAA level of non-dosed animals = 100 %). The results are shown in Table 5.

Table 5

Increasing effect on concentration of brain serotonin metabolite		
Test compound	Dose (mg/kg)	5-HIAA (%)
Compound A	100	150
Compound B	100	135

Experiment 7 Acute toxicity

A group of 5 male mice (Std-ddY strain, 25 - 30 g) was used. The test compound (200 mg/kg) was orally administered to the test animal in the form of a 0.5 % tragacanth solution or suspension, and for 7 days after the administration of the test compound, the lethality of animals was observed. As a result, no animal was died in the groups to which compounds A and B were administered.

The compounds of the present invention can be administered either in oral route, parenteral route or intrarectal route, but preferably in oral route. The dose of the compounds may vary depending on the kinds of the compounds, administration routes, severity of the disease and age of patients, but is usually in the range of 0.01 to 50 mg/kg/day, preferably 0.01 to 5 mg/kg/day.

The compounds of the present invention are usually administered in the form of a conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier or diluent. The pharmaceutically acceptable carrier or diluent includes the conventional pharmaceutically acceptable carriers or diluents which do not react with the compounds of the present invention. Suitable examples of the carrier or diluent are lactose, glucose, mannitol, sorbitol, dextrin, cyclodextrin, starch, sucrose, magnesium metasilicate aluminate, synthetic aluminum silicate, crystalline cellulose, sodium carboxymethyl cellulose, hydroxypropyl starch, calcium carboxymethyl cellulose, ion exchange resin, methyl cellulose, gelatin, acacia, pulluran, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, light silicic anhydride, magnesium stearate, talc, tragacanth, bentonite, veegum, carboxyvinyl polymer, titanium oxide, sorbitan fatty acid ester, sodium laurylsulfate, glycerin, glycerin fatty acid ester, anhydrous lanolin, glycerogelatin, polysorbate, macrogol, vegetable oil, wax, propylene glycol, water, and the like. The pharmaceutical preparation includes tablets, capsules, granules, fine granules, powders, syrups, suspensions, injections, suppositories, and the like. These preparations can be prepared by a conventional method. The liquid preparations may be in the form that they are dissolved or suspended in water or any other conventional medium when used. The tablets, granules and fine granules may be coated by a conventional coating agent. The injections are usually prepared by dissolving the compound of the present invention in water, but occasionally in a physiological saline solution or glucose solution, which is optionally incorporated with a buffer or a preservative. The pharmaceutical preparations may also contain other pharmaceutically active compounds.

The present invention is illustrated by the following Reference Examples, Examples and Preparations, but should not be construed to be limited thereto. The compounds are identified by elementary analysis, mass spectrum, IR spectrum, NMR spectrum, and the like.

Reference Example 1

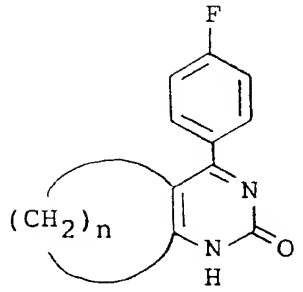
Preparation of 4-(4-fluorophenyl)-5,6,7,8-tetrahydro-2(1H)-quinazolinone:

A mixture of 2-(4-fluorobenzoyl)cyclohexanone (14 g), urea (7.6 g), conc. hydrochloric acid (8 ml) and ethanol (40 ml) is refluxed for 8 hours. After cooling, the reaction mixture is diluted with water and washed with methylene chloride. The aqueous layer is made alkaline with potassium carbonate, and the precipitated crystal is separated by filtration and recrystallized from N,N-dimethylformamide-ethanol to give the desired compound (9.6 g), m.p. 248 - 253 °C.

Reference Examples 2 to 4

In the same manner as described in Reference Example 1 except that the corresponding starting materials are used, there are obtained the compounds as shown in the following Table 6.

Table 6



Ref. Ex.	n	Melting point (°C)	Solvent for recrystallization
2	3	210 - 220	Ethanol
3	5	252 - 253	Methanol
4	6	257 - 262	Ethanol

Reference Example 5

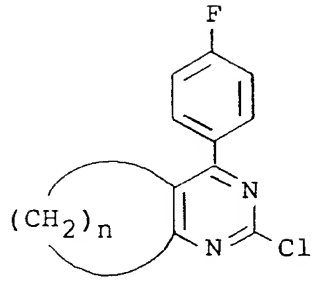
Preparation of 2-chloro-4-(4-fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidine:

To 4-(4-fluorophenyl)-1,5,6,7-tetrahydro-2H-cyclopentapyrimidin-2-one (14.3 g) is added phosphorus oxychloride (60 ml), and the mixture is refluxed for 5 hours. After cooling, the reaction mixture is diluted with chloroform (100 ml), and the mixture is added dropwise to ice-water over a period of 20 minutes. After the mixture is stirred for 30 minutes, the organic layer is separated, washed with water, dried over anhydrous sodium sulfate, and the solvent is distilled off under reduced pressure. The residue is dissolved in toluene and subjected to silica gel column chromatography. The fractions eluted with toluene are collected and the product therefrom is recrystallized from ethanol to give the desired compound (13.6 g), m.p. 106 - 107° C.

Reference Examples 6 to 7

In the same manner as described in Reference Example 5 except that the corresponding starting materials are used, there are obtained the compounds as shown in Table 7.

Table 7



Ref. Ex.	n	Melting point (°C)	Solvent for recrystallization
6	5	88 - 89	Hexane
7	6	124 - 125	Methylene chloride-hexane

The preparation of the compounds of the formula (I) of the present invention is illustrated by the following Examples.

Example 1

Preparation of 2-(1-piperazinyl)-4-(4-fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidine:

A mixture of 2-chloro-4-(4-fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidine (5.0 g), anhydrous piperazine (8.6 g), potassium iodide (3.3 g) and toluene (50 ml) is refluxed for 5 hours. After cooling, the reaction mixture is washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To the residue is added ethanol, and the insoluble materials are removed by filtration. To the filtrate is added a solution of maleic acid in methanol, and the resulting maleate product is recrystallized from methanol to give the maleate of the desired compound [compound A (4 g)], m.p. 185 - 186 °C.

Example 2

Preparation of 2-(1-piperazinyl)-4-(4-fluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine:

A mixture of 2-chloro-4-(4-fluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine (1.7 g), anhydrous piperazine (2.1 g) and dioxane (12 ml) is heated at 60 °C for 3 hours. After distilling off the solvent under reduced pressure, to the residue is added water and the mixture is extracted with chloroform. The extract is washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To the residue is added isopropyl alcohol and the insoluble materials are removed by filtration. To the filtrate is added a solution of maleic acid in ethanol, and the resulting maleate product is recrystallized from a mixture of methanol and isopropyl alcohol to give the maleate of the desired compound [compound B (1.4 g)], m.p. 202 - 203 °C.

Example 3

Preparation of 2-(1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclooctapyrimidine:

In the same manner as described in Example 1 except that the corresponding starting material is used, there is obtained the maleate of the desired compound (compound C), m.p. 189 - 191 °C (recrystallized from methanol-ethanol).

The preparation of the pharmaceutical composition of the present invention is illustrated by the following Preparations.

Preparation 1

Preparation of capsules:

Components	Amount
2-(1-Piperazinyl)-4-(4-fluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine maleate	10 g
Corn starch	52 g
Lactose	10 g
Crystalline cellulose	25 g
Hydroxypropyl cellulose	2 g
Light silicic anhydride	0.5 g
Magnesium stearate	0.5 g

According to a conventional method, the above components are mixed and granulated, and the granules thus obtained are packed in capsules (1000 capsules) to give capsules containing the granules of 100 mg per one capsule.

Preparation 2

Preparation of tablets:

Components	Amount
2-(1-Piperazinyl)-4-(4-fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidine maleate	10 g
Corn starch	15 g
Lactose	30 g
Crystalline cellulose	30 g
Hydroxypropyl cellulose	5 g
Low substituted hydroxypropyl cellulose	10 g

According to a conventional method, the above components are mixed and granulated, and the granules thus obtained are mixed with light silicic anhydride and magnesium stearate, and the mixture is tabletted to give tablets containing the active ingredient of 10 mg per one tablet.

Preparation 3

Preparation of powders:

Components	Amount
2-(1-Piperazinyl)-4-(4-fluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine maleate	10 g
Corn starch	168 g
Lactose	300 g
Hydroxypropyl cellulose	20 g

According to a conventional method, the above components are mixed, granulated and screened, and the granules thus obtained are mixed with an appropriate amount of light silicic anhydride to give powders (50 triturations).

Preparation 4

Preparation of injections:

Components	Amount
2-(1-Piperazinyl)-4-(4-fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidine maleate	10 g
D-Sorbitol	45 g
1N Aqueous solution of maleic acid or sodium hydroxide	q.s.
Distilled water for injection	q.s.
	Totally 1000 ml

The above active ingredient and D-sorbitol are mixed with distilled water for injection, and thereto is added 1N aqueous solution of maletic acid or sodium hydroxide to adjust the solution to pH 4.0. The solution is filterd with a membrane filter (pore size, 0.22 μm) and packed in ampoule (content 10 ml). The ampoule is sealed by melting and sterilized with high pressure steam at 121 °C for 20 minutes to give injection solutions.

Preparation 5

Preparation of lyophilized preparation:

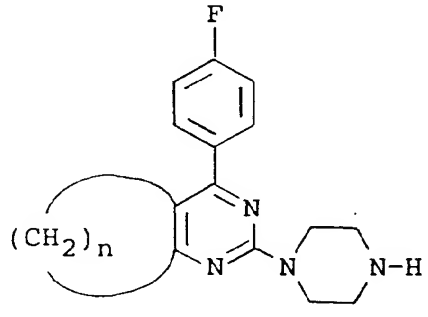
Components	Amount
2-(1-Piperazinyl)-4-(4-fluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine maleate	10 g
D-Mannitol	45 g
1N Aqueous solution of maleic acid of sodium hydroxide	q.s.
Distilled water for injection	q.s.
	Totally 1000 ml

The above active ingredient and D-mannitol are mixed with distilled water for injection, and thereto is added 1N aqueous solution of maleic acid or sodium hydroxide to adjust the solution to pH 4.0. The solution is filtered with a membrane filter (pore size, 0.22 μm) and packed in a vial (content 10 ml). The vial is sealed with a rubber stopper in halfway and subjected to lyophilization, that is, pre-freezing, primary drying at -50 °C, secondary drying at -20 °C, and then final drying at 20 °C. After completely sealed with a rubber stopper within a chamber, the vial is covered with a flip-off cap to give lyophilized preparation.

Claims

Claims for the Contracting States: AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE.

1. A compound of the formula:



(I)

wherein n is 3, 5 or 6, or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1, which is 2-(1-piperazinyl)-4-(4-fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidine, or a pharmaceutically acceptable acid addition salt thereof.

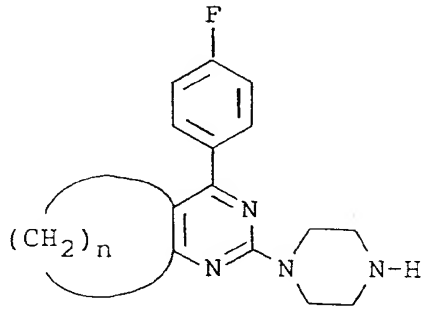
3. A compound according to claim 1, which is 2-(1-piperazinyl)-4-(4-fluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine, or a pharmaceutically acceptable acid addition salt thereof.

4. A compound according to claim 1, which is 2-(1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclooctapyrimidine, or a pharmaceutically acceptable acid addition salt thereof.

5. A pharmaceutical composition comprising a compound as set forth in any one of claims 1 to 4, or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

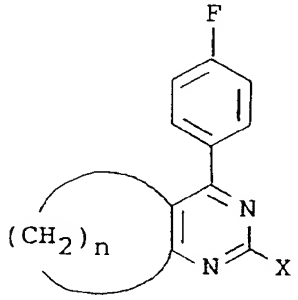
Claims for the Contracting State: ES

1. A process for preparing a compound of the formula:



(I)

wherein n is 3, 5 or 6, or a pharmaceutically acceptable acid addition salt thereof, characterized by reacting a compound of the formula (II):



(II)

wherein X is a leaving atom or group and n is as defined above, with piperazine and optionally converting the free form of the compound of the formula (II) into a pharmaceutically acceptable acid addition salt thereof.

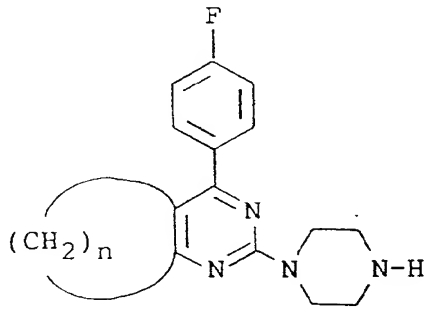
2. The process of claim 1 for the production of 2-(1-piperazinyl)-4-(4-fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidine, or a pharmaceutically acceptable acid addition salt thereof.

3. The process of claim 1 for the production of 2-(1-piperazinyl) 4-(4-fluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine, or a pharmaceutically acceptable acid addition salt thereof.

4. The process of claim 1 for the production of 2-(1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclooctapyrimidine, or a pharmaceutically acceptable acid addition salt thereof.

Claims for the Contracting State: GR

1. A compound of the formula:



(I)

wherein n is 3, 5 or 6, or an acid addition salt thereof.

2. A compound according to claim 1, which is 2-(1-piperazinyl)-4-(4-fluorophenyl)-6,7-dihydro-5H-cyclopentapyrimidine, or an acid addition salt thereof.

3. A compound according to claim 1, which is 2-(1-piperazinyl)-4-(4-fluorophenyl)-6,7,8,9-tetrahydro-5H-cycloheptapyrimidine, or an acid addition salt thereof.

4. A compound according to claim 1, which is 2-(1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclooctapyrimidine, or an acid addition salt thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 12 2107

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	EP-A-0 022 481 (MITSUBISHI) * claims 1,5-7 * ---	1-5	C07D239/84 C07D239/70 A61K31/505
D,A	US-A-3 915 976 (W. G. SALMOND) * column 1 - column 2; claim 1 * ---	1-5	
D,A	EP-A-0 302 967 (KANEBO) * page 6, line 16 - line 17; claims 1,2,5 * -----	1-5	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	03 MARCH 1992	FRANCOIS J.C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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